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(71) Applicant *(for all designated States except US)*: ELI LILLY AND COMPANY [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: LEVINE, Louise, R. [US/US]; 7590 Morningside Drive, Indianapolis, IN 46240 (US).

(74) Agents: HAY, Martin, A. et al.; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (US).

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(57) Abstract

Agonists which act at negatively–coupled cAMP–linked metabotropic glutamate receptors are useful for treating premenstrual dysphoric disorder.

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Treatment for Premenstrual Dysphoric Disorder

The present invention relates to the treatment of premenstrual dysphoric disorder.

Premenstrual dysphoric disorder is described on pages 715 to 718 of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DMS-IV), published by the American Psychiatric Association, Washington, DC, 1994. The condition is characterized by at least one of a markedly depressed mood, marked anxiety, marked affective ability and decreased interest in activities. These symptoms develop during the last week of the luteal phase of a menstrual cycle, and begin remission within a few days of the onset of the follicular phase (menses). Other symptoms which may develop are irritability, lack of concentration, fatigue, appetite change, disruption of normal sleep patterns, a sense of being out of control and physical symptoms such as breast tenderness or swelling, weight gain and pains. Females suffering from premenstrual dysphoric disorder commonly experience difficulties with personal relationships and in their jobs or schooling. Sometimes the symptoms are accompanied by thoughts of suicide. The condition is not restricted to menstruating females, and may also occur in non-menstruating females undergoing a cycle of luteal and follicular phases, for example females who have had a hysterectomy.

According to the DSM-IV, premenstrual dysphoric disorder is distinguishable from the premenstrual exacerbation of current mental disorders such as mood disorders and anxiety disorders. The latter disorders persist throughout the menstrual cycle, although the symptoms may present most acutely during the premenstrual phase.

A variety of different drugs has been shown to be efficacious in the treatment of premenstrual dysphoric

disorder, but each of these has associated side effects which limits its applicability. These treatments are reviewed by Margaret L. Moline in Therapy Reviews, *Clinical Pharmacy*, Vol. 12, 1993, pp 181-196 and Joseph F. Mortola, *Drug Safety*, 10(2): 160-169, 1994.

International patent application publication number W096/04901 discloses that compounds which act at negatively-coupled cAMP-linked metabotropic glutamate receptors are useful for the treatment of anxiety and related disorders.

The present invention provides a method of treating premenstrual dysphoric disorder, which comprises administering to a female subject in need of treatment an effective amount of an agonist which acts at negatively-coupled cAMP-linked metabotropic glutamate receptors.

According to another aspect, the present invention provides the use of an agonist which acts at negatively coupled cAMP-linked metabotropic glutamate receptors for the manufacture of a medicament for the treatment of premenstrual dysphoric disorder.

According to yet another aspect, the present invention provides a pharmaceutical composition for use in the treatment of premenstrual dysphoric disorder, which comprises an agonist which acts at negatively-coupled cAMP-linked metabotropic glutamate receptors.

The particular dose of agonist administered according to this invention will of course be determined by the particular circumstances surrounding the case, including the activity of the particular agonist administered, the route of administration, the particular condition being treated, and similar considerations. The agonist can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, or intranasal routes. Alternatively, the agonist may be administered by continuous infusion. A typical daily dose will contain from about 0.001 mg/kg to about 100 mg/kg of the agonist. Preferably, daily doses will be about 0.05 mg/kg to about 50

mg/kg, more preferably from about 0.1 mg/kg to about 20 mg/kg.

The agonist is preferably formulated prior to administration in combination with one or more pharmaceutically-acceptable carriers, diluents, or excipients. The pharmaceutical formulations are prepared by known procedures using well-known and readily available ingredients. In making the compositions, the active ingredient will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier, and may be in the form of a capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be a solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active ingredient. The compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols, ointments containing, for example, up to 10% by weight of active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, dermal patch, subcutaneous implant, and sterile packaged powders.

Some examples of suitable carriers, excipients, and diluents include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum, acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water syrup, methyl cellulose, methyl and propyl hydroxybenzoates, talc, magnesium stearate, stearic acid, and mineral oil. The formulations can additionally include lubricating agents, wetting agents (surfactants), emulsifying and suspending agents, preserving agents, sweetening agents, or flavoring agents. Compositions may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 1 mg to about 500 mg, more preferably about 5 mg to about 200 mg of the active ingredient. The term "unit dosage form" refers to a physically discrete unit suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier, diluent, or excipient. The following formulation examples are illustrative only and are not intended to limit the scope of the invention in any way.

Formulation 1

Tablets each containing 60 mg of agonist are made as follows:

Agonist	60 mg
Starch	45 mg
Microcrystalline cellulose	35 mg
Polyvinylpyrrolidone	4 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1 mg
Total	150 mg

The agonist, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

Formulation 2

Capsules each containing 80 mg of agonist are made as follows:

Agonist	80 mg
Starch	59 mg
Microcrystalline cellulose	59 mg
Magnesium stearate	2 mg
Total	200 mg

The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 45 sieve, and filled into hard gelatin capsules in 200 mg quantities.

Agonists which act at negatively coupled cAMP-linked metabotropic glutamate receptors may be identified using the following experiment. Firstly, the affinity of a test compound for metabotropic glutamate receptors may be demonstrated by the selective displacement of (1*S*,3*R*)-1-aminocyclopentane-1,3-dicarboxylic acid-sensitive [^{3}H]glutamate binding to rat brain cell membranes. The binding of [^{3}H]glutamate ([^{3}H]Glu) is conducted with crude membranes of rat forebrain as described by Schoepp and True. Schoepp and True, *Neuroscience Lett.*, **145**, 100-104 (1992); Wright, McDonald, and Schoepp, *J. Neurochem.*, **63**, 938-945 (1994). The affinity of a test compound for the receptor may be expressed as the concentration of the test compound that inhibits 50% binding (IC_{50}), or the percent displacement of [^{3}H]Glu at a 10 μM or 100 μM concentration of the formula I compound.

The ability of a test compound to act as an agonist at negatively coupled cAMP-linked metabotropic receptors may be measured using the following method. Test compounds are tested for their ability to decrease forskolin-stimulated cAMP formation in the rat hippocampus and the rat cerebral cortex, using the procedures described in Schoepp and

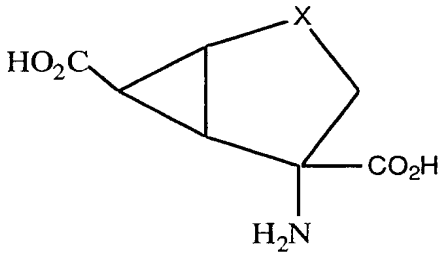
Johnson. Schoepp and Johnson, *Neurochem. Int.*, **22**, 277-283 (1993).

The effectiveness of an agonist that acts at negatively coupled metabotropic glutamate receptors to treat premenstrual dysphoric disorder is demonstrated in the following clinical study.

Three to fifty women are selected for the clinical study. The women have regular menses, are in good general health, and suffer from one or more of the above mentioned PMS symptoms. Because of the somewhat idiosyncratic and subjective nature of these symptoms, the study has a placebo control group, i.e., the women are divided into two groups, one of which receives the agonist (the active agent of this invention), and the other receives a placebo. Women in the test group receive between 10-400 mg of the drug per day by the oral route. They continue this therapy for 1-3 months. Accurate records are kept as to the number and severity of the symptoms in both groups and at the end of the study these results are compared. The results are compared both between members of each group and also the results for each patient are compared to the symptoms reported by each patient before the study began.

The effectiveness of the invention is illustrated by the positive impact observed on one or more of the symptoms of premenstrual dysphoric disorder in a study as described above.

The agonist which acts at negatively-coupled cAMP-linked metabotropic glutamate receptors may be a compound of the formula



I

in which X represents CH_2, O or S, or a pharmaceutically acceptable metabolically labile ester or amide thereof, or a pharmaceutically acceptable salt thereof.

Preferred compounds of formula I are:

1S,2S,5R,6S-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid;

1SR,4SR,5RS,6SR-4-amino-2-oxabicyclo[3.1.0]hexane-4,6-dicarboxylic acid;

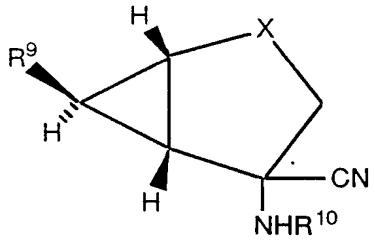
1SR,4SR,5RS,6SR-4-amino-2-thiabicyclo[3.1.0]hexane-4,6-dicarboxylic acid and

1R,4R,5S,6R-4-amino-2-oxabicyclo[3.1.0]hexane-4,6-dicarboxylic acid.

The compounds of formula I in which X represents CH_2, and their esters, amides and salts may be prepared as described in European patent application publication number EP-A-696577.

The compounds of formula I in which X represents O or S may be prepared by a process which comprises

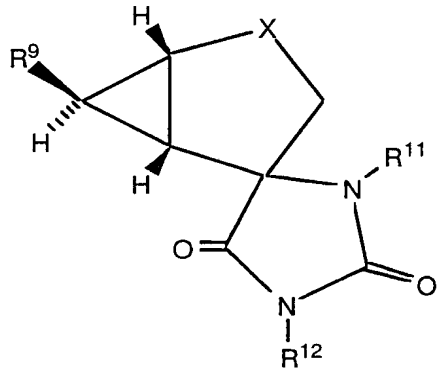
(a) hydrolyzing a compound of formula



II

in which R^{10} represents a hydrogen atom or an acyl group and R^9 represents a carboxyl group or an esterified carboxyl group, or a salt thereof;

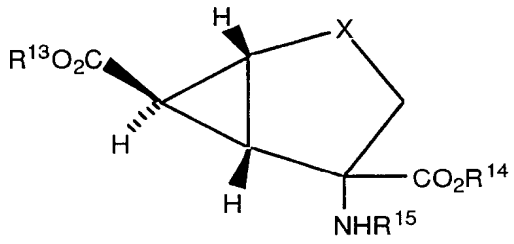
(b) hydrolyzing a compound of formula



III

in which R^9 represents a carboxyl group or an esterified carboxyl group, and R^{11} and R^{12} each independently represent a hydrogen atom, a (2-6C) alkanoyl group, a (1-4C) alkyl group, a (3-4C) alkenyl group or a phenyl (1-4C) alkyl group in which the phenyl is unsubstituted or substituted by halogen, (1-4C) alkyl or (1-4C) alkoxy, or a salt thereof; or

(c) deprotecting a compound of formula



IV

in which R^{15} represents a hydrogen atom or a nitrogen protecting group and each of R^{13} and R^{14} independently represents a hydrogen atom or a carboxyl protecting group, or a salt thereof;

whereafter, if necessary and/or desired

(i) resolving the compound of formula I;

(ii) converting the compound of formula I into a non-toxic metabolically labile ester or amide thereof; and/or;

(iii) converting the compound of formula I or a non-toxic metabolically labile ester or amide thereof into a pharmaceutically acceptable salt thereof.

The protection of carboxylic acid and amine groups is generally described in McOmie, Protecting Groups in Organic Chemistry, Plenum Press, NY, 1973, and Greene and Wuts, Protecting Groups in Organic Synthesis, 2nd. Ed., John Wiley & Sons, NY, 1991. Examples of carboxy protecting groups include alkyl groups such as methyl, ethyl, *t*-butyl and *t*-amyl; aralkyl groups such as benzyl, 4-nitrobenzyl, 4-methoxybenzyl, 3,4-dimethoxybenzyl, 2,4-dimethoxybenzyl, 2,4,6-trimethoxybenzyl, 2,4,6-trimethylbenzyl, benzhydryl and trityl; silyl groups such as trimethylsilyl and *t*-butyldimethylsilyl; and allyl groups such as allyl and 1-(trimethylsilylmethyl)prop-1-en-3-yl. Examples of amine protecting groups include acyl groups, such as groups of formula $R^{11}CO$ in which R^{11} represents (1-6C) alkyl, (3-10C) cycloalkyl, phenyl(1-6C) alkyl, phenyl, (1-6C) alkoxy, phenyl(1-6C)alkoxy, or a (3-10C) cycloalkoxy, wherein a phenyl group may optionally be substituted by one or two substituents independently selected from amino, hydroxy, nitro, halogeno, (1-6C) alkyl, (1-6C) alkoxy, carboxy, (1-6C) alkoxycarbonyl, carbamoyl, (1-6C) alkanoylamino, (1-6C) alkylsulphonylamino, phenylsulphonylamino, toluenesulphonyl-amino, and (1-6C)fluoroalkyl.

The compounds of formula II are conveniently hydrolyzed in the presence of an acid, such as hydrochloric acid or sulfuric acid, or a base, such as an alkali metal hydroxide, for example sodium hydroxide. The hydrolysis is conveniently performed in an aqueous solvent such as water and at a temperature in the range of from 50 to 200_C.

The compounds of formula III are conveniently hydrolyzed in the presence of a base, for example an alkali metal hydroxide such as lithium, sodium or potassium hydroxide, or an alkaline earth metal hydroxide such as

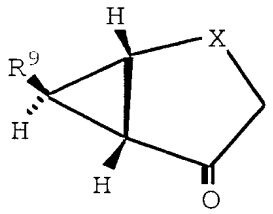
barium hydroxide. Suitable reaction media include water. The temperature is conveniently in the range of from 50 to 150 °C.

Preferred values for R^{10} are hydrogen and (2-6C)alkanoyl groups, such as acetyl.

Preferred values for R^{9} when it represents an esterified carboxyl group are (1-6C)alkoxycarbonyl groups such as ethoxycarbonyl.

The compounds of formula IV may be deprotected by a conventional method. Thus, an alkyl carboxyl protecting group may be removed by hydrolysis. The hydrolysis may conveniently be performed by heating the compound of formula V in the presence of either a base, for example an alkali metal hydroxide such as lithium, sodium or potassium hydroxide, or an alkaline metal hydroxide, such as barium hydroxide, or an acid such as hydrochloric acid. The hydrolysis is conveniently performed at a temperature in the range of from 10 to 300 °C. An aralkyl carboxyl protecting group may conveniently be removed by hydrogenation. The hydrogenation may conveniently be effected by reacting the compound of formula V with hydrogen in the presence of a Group VIII metal catalyst, for example a palladium catalyst such as palladium on charcoal. Suitable solvents for the reaction include alcohols such as ethanol. The reaction is conveniently performed at a temperature in the range of from 0 to 100°C. An acyl, amine protecting group is also conveniently removed by hydrolysis, for example as described for the removal of an alkyl carboxyl protecting group.

The compounds of formula II may be prepared by reacting a compound of formula V



V

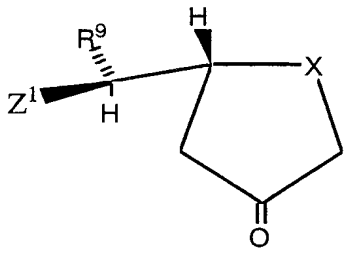
with an alkali metal cyanide, such as lithium, sodium or potassium cyanide, and an ammonium halide, such as ammonium chloride, conveniently in the presence of ultrasound. Thus, the ammonium halide is mixed with chromatography grade alumina in the presence of a suitable diluent such as acetonitrile. The mixture is then irradiated with ultrasound, whereafter the compound of formula V is added, and the mixture is again irradiated. The alkali metal cyanide is then added, followed by further irradiation with ultrasound.

The resultant mixture of diastereoisomeric aminonitriles is then reacted with an acylating agent, such as acetyl chloride in the presence of a suitable base, for example an amine such as ethyl diisopropylamine and in the presence of a suitable solvent, such as dichloromethane, to afford a mixture of diastereomeric acylamino nitriles. The desired diastereoisomer is conveniently separated from this mixture, for example by chromatography.

The compounds of formula III may be prepared by reacting a compound of formula V with an alkali metal cyanide, such as lithium, sodium or potassium cyanide, and ammonium carbonate or ammonium carbamate. Convenient solvents include alcohols, such as methanol, aqueous methanol and aqueous ethanol. Conveniently the reaction is performed at a temperature in the range of from 10 to 150°C. If desired, the compounds of formula III may then be alkylated, for example using an appropriate compound of formula $R^{11}Cl$ and/or $R^{12}Cl$.

The compounds of formula III may conveniently be resolved prior to hydrolysis. Thus, for example, a compound of formula III in which R^9 represents a carboxyl group may be resolved by treatment with an optically active amine, such as (R)-2-phenylglycinol.

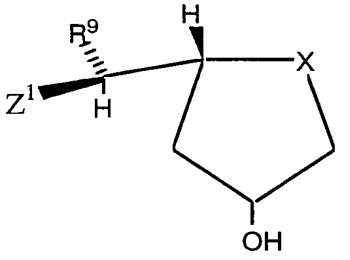
The compounds of formula V in which X represents O may be prepared by cyclising a compound of formula



VI

in which Z^1 represents a leaving atom or group, for example an iodine atom. The reaction is conveniently performed in the presence of a base, such as 1,8-diazabicyclo[5.4.0]undec-7-ene. Suitable solvents include ethers, such as tetrahydrofuran. The temperature is conveniently in the range of from 0 to 100_C.

The compounds of formula VI may be prepared by oxidising a compound of formula

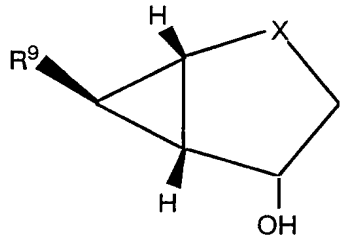


VIa

The oxidation is conveniently effected using an appropriate conventional oxidation method, for example, using oxalyl chloride in dimethyl sulfoxide or (when X is O only) chromium trioxide in sulfuric acid (Jones reagent).

The compounds of formula VIa may be prepared by the method described in J. Amer. Chem. Soc., 110 (14), 1988, pages 4533-4540.

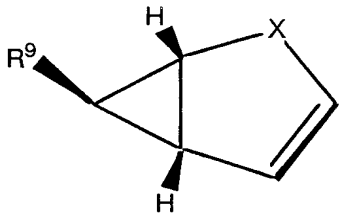
The compound of formula V may also be prepared by oxidizing a compound of formula



VII

The oxidation may conveniently be effected by reacting the compounds of formula VII with dimethyl sulfoxide in the presence of an activating agent, such as oxalyl chloride, followed by treatment with a base, such as triethylamine. The reaction is conveniently performed at a temperature in the range of from -80 to -20°C.

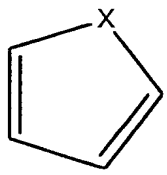
The compounds of formula VII may be prepared by reacting a compound of formula



IX

with a hydroborating agent, such as borane or thexylborane, followed by an oxidizing agent, such as hydrogen peroxide in the presence of a base, such as sodium hydroxide or an aqueous buffer in the pH range of from 5 to 14. The temperature is conveniently in the range of from -20 to 25°C. The reaction may generally be performed according to the methods described in J. Am. Chem. Soc. 1986, 108, 2049 and J. Am. Chem. Soc., 1991, 113, 4037.

The compounds of formula IX may be prepared by reacting a compound of formula



X

with a compound of formula R^9CN_2 in the presence of a transition metal catalyst, such as a rhodium or copper catalyst. The reaction may generally be performed according to the methods described in J. Chem. Soc. Perkin Tran I, 1979, 2624; Tetrahedron, 1971, 27, 2957. Justus Liebigs Ann. Chem. 1963, 668, 19; and Tet. Let. 1964, 2185.

The following examples illustrate the preparation of compounds of formula I.

Example 1

1SR,4SR,5RS,6SR-4-Amino-2-Oxabicyclo[3.1.0]hexane-4,6-dicarboxylic Acid

(a) 2SR-1,2-*O*-Isopropylidene-butane-1,2,4-triol. A solution of 1,2,4-butanetriol (53 g, 500 mmol) in acetone (1L) was treated in one portion with p-toluenesulfonic acid monohydrate (4.75 g, 25 mmol) and stirred at ambient temperature overnight. Triethylamine (2.5 g, 25 mmol) was added in one portion and the resulting reaction mixture concentrated in vacuo to yield the crude product. Purification via HPLC (10% EtOAc/hexanes to 50% EtOAC/-hexanes) afforded the title compound (53.1 g, 363 mmol) 73%. FDMS: $M^+ + 1 = 147$. Anal. calcd. for $C_7H_{14}O_3 \cdot 0.5\ H_2O$: C, 54.18; H, 9.74. Found: C, 54.50; H, 9.56.

(b) 5SR,E-Ethyl 5,6-*O*-Isopropylidene-5,6-dihydroxy-2-hexenoate. (DMSO (56.65 g, 725 mmol) was added dropwise to a -78°C solution of oxalyl chloride (48.32 g, 380.7 mmol) in CH_2Cl_2 (1L) and stirred for 15 minutes. Subsequently, a solution of the product of step (a) (53 g, 362.6 mmol) in CH_2Cl_2 (400 mL) was added dropwise at a rate to maintain reaction temperature ² -60°C. N,N-Diisopropylethylamine (140.6 g, 1087 mmol) was added dropwise and the resulting slurry allowed to warm to ambient temperature as it stirred for 2 hours to afford crude *O*-Isopropylidene-4-oxo-(*SR*)butane-1,2-diol. The reaction mixture was chilled to 0°

C, (carbethoxymethylene)-triphenylphosphorane (252.5 g, 725 mmol) was added in one portion, and allowed to warm to ambient temperature as it stirred overnight. The reaction mixture was diluted with diethylether, washed consecutively with H_2O, aqueous $NaHSO_4$, and brine, dried over $MgSO_4$ and concentrated in vacuo to yield the crude product. The product was triturated in Et_2O, the $Ph_3P=O$ removed via filtration, and the filtrate concentrated in vacuo to yield the crude product. Purification via HPLC (10% EtOAc/hexanes to 50% EtOAC/hexanes) afforded the Z isomer (1.52 g, 7.1 mmol) 2% and the title E isomer (56.55 g, 264 mmol) 73%. Z Isomer: FDMS: $M^+ + 1 = 215$. Anal. calcd. for $C_{11}H_{18}O_4 \cdot 0.25 H_2O$: C, 60.39; H, 8.52. Found: C, 60.49; H, 8.28. E isomer: FDMS: $M^+ + 1 = 215$. Anal. calcd. for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.44; H, 8.24.

(c) 5SR.E-Ethyl (*SR*, E) 5,6-Dihydroxy-2-hexenoate. A solution of the product of step (b) (46.4 g, 216.6 mmol) in THF (700 mL) was treated in one portion with 1N HCl (500 mL) and stirred at ambient temperature overnight. EtOAc and NaCl were added and the resulting slurry stirred vigorously for two hours. The reaction mixture was partitioned in a separatory funnel and the product extracted with EtOAc. All organics were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo to yield the crude diol. Purification via HPLC (25% EtOAc/hexanes to 95% EtOAc/hexanes) afforded the title compound (30.52 g, 175 mmol) 81%. FDMS: $M^+ + 1 = 175$. Anal. calcd. for $C_8H_{14}O_4 \cdot 0.25 H_2O$: C, 53.77; H, 8.18. Found: C, 53.88; H, 7.95.

(d) 2SR,4RS-Ethyl 2-[(4-Hydroxytetrahydrofuran-2-yl)]-2-iodoacetate. A solution of the product of step (c) (30.41 g, 174.6 mmol) in diethyl ether (1.5 L) at ambient temperature was treated consecutively with $NaHCO_3$ (44.0 g, 524 mmol) then I_2 (100.8 g, 788 mmol), and the resulting reaction mixture stirred until complete by TLC. Aqueous $Na_2S_2O_3$ was added to the reaction mixture and product extracted with Et_2O. All organics were combined, washed with $Na_2S_2O_3$, H_2O, then brine, dried over Na_2SO_4 and concentrated in vacuo to yield the crude product. Purification via HPLC (5% EtOAc/hexanes to 50% EtOAc/hexanes) afforded the title compound (29.05 g, 97 mmol) 55%. FDMS: $M^+ + 1 = 301$. Anal. calcd. for $C_8H_{13}IO_4 \cdot 1.0\ H_2O$: C, 30.21; H, 4.75. Found: C, 30.23; H, 4.43.

(e) 2SR-Ethyl 2-[(4-oxo-tetrahydrofuran-2-yl)]-iodoacetate. A solution of the product of step (d) (28.5 g, 95 mmol) in CH_2Cl_2 (500 mL) with 3Å sieves was treated in one portion with pyridinium chlorochromate (91.5 g, 425 mmol) and stirred at ambient temperature overnight. The reaction mixture was diluted with Et_2O and filtered through celite®. The filtrate was partitioned with 1N HCl and the product extracted with Et_2O. All organics were combined, washed with 1N HCl, and brine, dried over MgSO4, and concentrated in vacuo to yield the crude product. Purification via HPLC (10% EtOAc/hexanes to 50% EtOAc/hexanes) afforded the title compound (17.9 g, 60.1 mmol) 63%. FDMS: $M^+ = 298$. Anal. calcd. for $C_8H_{11}IO_4 \cdot 0.5\ H_2O$: C, 31.29; H, 3.94. Found: C, 31.16; H, 3.75.

(f) 1SR,5SR,6SR-Ethyl 2-oxabicyclo[3.1.0]hexan-4-one-6-carboxylate. A solution of the product of step (e) (5.25 g, 17.6 mmol) in THF (50 mL) was treated by dropwise addition of a solution DBU (2.82 g, 18.5 mmol) in THF (10 mL) and the resulting reaction mixture stirred at ambient temperature for 1 hour. The reaction mixture was reduced in vacuo,

partitioned between Et_2O and 1N HCl, and the product extracted with Et_2O. All organics were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo to yield the crude product. Purification via HPLC (10% EtOAc/hexanes to 50 % EtOAc/hexanes) afforded the title compound (1.47 g, 8.63 mmol) 49%. FDMS: M^+ = 170 Anal. calcd. for $C_8H_{10}O_4 \cdot 0.1\ H_2O$: C, 55.88; H, 5.98. Found: C, 55.73; H, 5.81.

(g) 1SR,4SR,5RS,6SR-Diethyl 4-(aminobenzyloxycarbonyl)-2-oxabicyclo[3.1.0]- hexane-4,6-dicarboxylate. A solution of the product of step (f) (3.0 g, 17.6 mmol) in a 1:1 mixture of EtOH:H_2O (50 mL total volume) was treated consecutively with $NH_2CO_2NH_4$ (4.13 g, 52.9 mmol), then KCN (1.72 g, 26.4 mmol) and warmed at 55°C for 40 hours. NaOH (4.0 g, 100 mmol) added in one portion to the reaction and warmed under reflux for 48 hours. The reaction mixture was concentrated in vacuo and the crude aminodiacid reconstituted in H_2O. The aqueous component was washed with Et_2O (3X), chilled to 0°C, and acidified to pH = 1 with conc. HCl. The aqueous component was washed with Et_2O (3X), basified to pH = 10 with $NaHCO_3$, and concentrated to dryness *in vacuo*. The solids were reconstituted in a 1:1 mixture of THF:H_2O (100 mL total volume), stirred at 0°C as benzylchloroformate (4.50 g, 26.4 mmol) was added dropwise, and allowed to warm to ambient temperature as it stirred for 48 hours. The reaction mixture was diluted and washed with Et_2O. The aqueous layer was acidified to pH = 1 with conc. HCl, and partitioned with NaCl and EtOAc. The product was extracted with EtOAc, dried over MgSO4, and concentrated in vacuo to yield the crude N-CBZ diacid. This intermediate was reconstituted in CH_3CN and treated consecutively with triethylamine (5.6 g 56 mmol) then iodoethane (6.5 g, 42 mmol) and warmed at 50°C for 48 hours. The reaction mixture was diluted with Et_2O and partitioned with 1N HCl. The product was extracted with Et_2O, washed with brine, dried over MgSO4 and concentrated in vacuo to yield the crude

product which was purified by HPLC (10% EtOAc/hexanes to 50% EtOAc/hexanes) to afford the title compound (1.18 g, 3.13 mmol) 18%. FDMS: M^+ = 377 Anal. calcd. for $C_{19}H_{23}NO_7$: C, 60.47; H, 6.14; N, 3.71. Found: C, 60.61; H, 6.44; N, 3.75.

(h) A solution of the product of step (g) (0.71 g, 1.86 mmol) in 2N NaOH (20 mL) was warmed under reflux for 3 days. The reaction mixture was partitioned and washed with EtOAc. The resulting aqueous component was subsequently acidified with 6N HCl and washed with EtOAc. All organics were discarded. The aqueous phase was concentrated to dryness, reconstituted in H_2O and the pH adjusted to 14 with 1N NaOH. The resulting solids were removed by filtration and the filtrate reduced *in vacuo*. The pH was adjusted to 2 with 1 N HCl, applied to Dowex® 50X8-100 cation exchange resin and eluted with 10% pyridine/H_2O to afford the title compound (0.25 g, 1.34 mmol) 72%. mp = dec >200°C. FDMS: $M^+ + 1$ = 188. Anal. calcd. for $C_7H_9NO_5$: C, 44.92; H, 4.85; N, 7.48. Found: C, 44.69; H, 4.73; N, 7.25.

Example 2

1SR,4RS,5RS,6RS-4-Amino-2-Thiabicyclo[3.1.0]hexane-4,6-dicarboxylic Acid

(a) (1*SR*,5*RS*,6*RS*)-Ethyl [2-thiabicyclo[3.1.0]hex-3-ene]-carboxylate. A solution of ethyldiazoacetate (11.4 g, 100 mmol) in thiophene (20 mL) was added dropwise to a 70°C solution of $[Rh(OAc)_2]_2$ in thiophene (100 mL). Upon complete addition, the reaction mixture was warmed under reflux for 3 hours, concentrated to an orange oil and purified by prep HPLC (10% EtOAc/hexanes) to afford 6.51 g (38%, 38.2 mmol) of the title compound. FDMS: M^+ = 170. Anal. calcd. for $C_8H_{10}O_2S$: C, 56.45; H, 5.92; S, 18.84. Found: C, 56.72; H, 6.21; S, 19.11.

(b) (1*SR*,4*RS*,5*RS*,6*RS*)-Ethyl 4-hydroxy-[2-thiabicyclo[3.1.0]-hexane] carboxylate. A solution of BH_3·THF (1M, 5.3 mmol) was added dropwise to a 0°C solution of the product of step (a) (0.90 g, 5.29 mmol) in THF (25 mL), and subsequently stirred at 0°C for 6 hours. 3N NaOH (5 mL) was added dropwise follwed by 30% H_2O_2 (1 mL). The resulting reaction mixture was allowed to warm to ambient temperature as it stirred overnight. The reaction was partitioned with saturated $NaHCO_3$ and the product extracted with Et_2O. All organics were combined, washed with brine, dried ($MgSO_4$), and purified by PC-TLC (10% EtOAc/hexanes to 50% EtOAc/hexanes) to afford 0.48 g (48%, 2.5 mmol) of the title compound. FDMS: M^+ = 188. Anal. calcd. for $C_8H_{12}O_3S$·0.4 H2O: C, 49.16; H, 6.60; S, 16.40. Found: C, 49.03; H, 6.28; S, 17.80.

(c) (1*SR*,5*RS*,6*RS*)-Ethyl 4-oxo-[2-thiabicyclo[3.1.0]hexane] carboxylate. Oxalyl chloride (4.35 g, 34.3 mmol) was added dropwise to a -78°C solution of DMSO (3.56 g, 45.6 mmol) in CH_2Cl_2 (400 mL) at a rate to maintain reaction temperature ² -65°C. Upon complete addition the reaction was allowed to equilibrate for 30 minutes, followed by dropwise addition of a solution of the product of step (b) (4.31 g, 22.8 mmol) in CH_2Cl_2 (20 mL) maintaining reaction temperature ² -65°C. The reaction was allowed to slowly warm to -40°C, after which time the reaction was once again chilled to -78°C, and quenched by dropwise addition of triethylamine (11.54 g, 114 mmol). The reaction was partitioned with 1N HCl and NaCl and the product extracted with Et_2O. All organic phases were combined, washed with H_2O, and brine, dried ($MgSO_4$) and purified by prep HPLC (10 % EtOAc/hexanes to 50% EtOAc/ hexanes) to afford 3.20 g (17.2 mmol, 75%) of the title compound. mp = 55 - 57°C. FDMS: M^+ = 186. Anal. calcd. for $C_8H_{10}O_3S$: C, 51.60; H, 5.41; S, 17.23. Found: C, 51.59; H, 5.32; S, 17.63.

(d) (1*SR*,4*RS*,5*RS*,6*RS*)-Ethyl 4-(spiro-5'-hydantoin)-[2-thiabicyclo[3.1.0]hexane] carboxylate. A solution of the product from step (c) (3.22 g, 17.3 mmol) in EtOH (25 mL) and H_2O (10 mL) at ambient temperature, was treated consecutively with $(NH_4)_2CO_3$ (3.37 g, 43.3 mmol), and KCN (1.41 g, 21.6 mmol) and warmed at 35°C until reaction judged complete by TLC. The reaction mixture was acidified with 6N HCl, partitioned with NaCl and the product extracted with EtOAc. All organics were combined, dried ($MgSO_4$), and recrystallized from 2-propanol to afford 2.25 g (8.8 mmol, 51%) of the title compound. mp = 197 - 200°C. FDMS: M^+ = 256. Anal. calcd. for $C_{10}H_{12}N_2O_4S \cdot 0.75$ IPA: C, 48.83; H, 6.02; N, 9.30. Found: C, 48.75; H, 6.07; N, 8.94.

(e) (1*SR*,4*RS*,5*RS*,6*RS*) 4-Amino[2-thiabicyco[3.1.0]hexane]-4,6-dicarboxylate. A solution of the product from step (d) (0.85 g, 3.30 mmol) in 2N NaOH (20 mL) was warmed under reflux for 4 days. The reaction mixture was then acidified with 6N HCl and concentrated to dryness. The solid was reconstituted in H2O at pH = 11, applied to Bio-Rad® AG1-X8 anion exchange resin, eluted with 3N AcOH, and concentrated to dryness. The product was triturated in hot H2O/2-propanol mixture and filtered to afford 0.31 g, (46%, 1.5 mmol) of the title compound. mp > 250°C. FDMS: M^+ = 203. Anal. calcd. for $C_7H_9NO_4S \cdot 0.5$ H2O: C, 39.62; H, 4.75; N, 6.60; S, 15.11. Found: C, 39.81; H, 4.48; N, 6.69; S, 14.27.

Example 3

1R,4R,5S,6R-4-Amino-2-Oxabicyclo[3.1.0]hexane-4,6-dicarboxylic Acid

(a) (1SR, 5SR, 6SR)-Ethyl-[2-oxabicyclo[3.1.0]hex-3-ene carboxylate. A solution of ethyldiazoacetate (100 g) in furan (250 mL) was added dropwise to a solution of $[Rh(OAc)_2]_2$ in furan (250 mL) with stirring at 10°C over a period of about 2 to 2.5 hours. A further 0.1 g of $[Rh(OAc)_2]_2$ was added about two thirds of the way into the addition. After HPLC analysis showed complete consumption of ethyldiazoacetate, a solution of $NaHSO_3$ (200 g) in water (400 mL) was added, and the resultant two phase mixture was allowed to warm to ambient temperature with stirring for 1 to 2 hours. The reaction mixture was then extracted with MTBG (500 mL), and the organic phase washed with water (400 mL) and saturated NaCl (300 mL), then dried over Na_2SO_4. The solvent was then removed by evaporation, and the resultant oil was vacuum distilled (45°C at 0.2 mm Hg) to afford the title compound (47-54 g) as an oil.

(b) (1SR, 4RS, 5SR, 6SR)-Ethyl-4-hydroxy-[2-oxabicyclo-[3.1.0]hexane]carboxylate. A solution of thexylborane was prepared by adding a solution of 2,3-dimethyl-2-butene (4M, 53.0 mL) in THF via a syringe to borane dimethyl sulfide complex (10 M, 21.2 mL) in a dry flask under nitrogen at below 0°C. The solution was stirred for 2 hours at <0°C before use.

The product of step (a) (32.73 g, 212.30 mmol) was dissolved in 150 mL of THF under N_2. The resultant solution was cooled with stirring to -0.5°C. While the stirring solution was cooling, the system was evacuated and purged with N_2 twice. The entire thexylborane solution prepared above was added via cannula over 40 minutes, maintaining the temperature <4.4°C. After stirring 2 hours at 0°C, 87 mL of 30% H_2O_2 was added slowly, over 70 minutes, to maintain the

temperature at <30°C. Following the peroxide addition, 15 mL of pH = 7 phosphate buffer (1M KH_2PO_4 and 1M in K_2HPO_4) was added and the mixture was allowed to stir overnight (14 hours) while warming to ambient temperature. The mixture was cooled <5°C and 25 mL of saturated aqueous $Na_2S_2O_3$ was added slowly. 75 mL of EtOAc was then added, followed slowly by 75 mL of saturated aqueous $Na_2S_2O_3$. Another 40 mL of saturated aqueous $Na_2S_2O_3$ was then added slowly. The mixture was stirred for 15 minutes, then partitioned between 75 mL of EtOAc and 30 mL of saturated aqueous $Na_2S_2O_3$. The aqueous layer was back extracted three times with 50 mL of EtOAc. The combined organic layers were washed with 30 mL of brine and dried over Na_2SO_4. The solvent was removed to afford 54.44 g of an oil. The oil was purified by a flash chromatography (370 g of silica gel, wet packed with 3:2 hexanes: EtOAc) eluting with 3:2 hexanes: EtOAc, to afford 31.72 g of the title compound as an oil.

(c) (1SR, 5SR, 6SR)-Ethyl 4-oxo-[2-oxabicyclo[3.1.0]-hexane]carboxylate. Oxalyl chloride (25.70 g, 202.44 mmol) in CH_2Cl_2 (300 mL) under N_2 was added dropwise over 35 minutes to a solution of DMSO (28.74 g, 367.8 mmol) while keeping the temperature below <-65°C. The solution was stirred for 10 minutes, and cooled back to -70°C. A solution of 31.68 g of the product of step (b) (26.29 g, 152.71 mmol corrected for 83% potency) dissolved in 100 mL of CH_2Cl_2 was added dropwise over 40 minutes while maintaining the temperature at -67°C. The mixture was stirred for 5 minutes, then 62 mL (45.01 g, 444.83 mmol) of triethylamine was added dropwise over 15 minutes, keeping the temperature below -50°C. After stirring for 15 minutes, TLC indicated complete reaction and the mixture allowed to warm to about -40°C. The mixture was filtered, and washed through with 300 mL of CH_2Cl_2. The filtrate was extracted two times with 150 mL of 1N HCl. The aqueous layer was back extracted with 50 mL of CH_2Cl_2. The combined organic layers

were washed with 75 mL of brine and dried over Na_2SO_4. Most of the solvent was removed by rotary evaporation to leave 44.36 g of liquid. A few seed crystals were added and the flask was blanketed with N_2 and stirred ambient temperature for 30 minutes while a thin slurry formed. To the room temperature slurry was slowly added 20 mL of hexanes. The slurry was stirred 90 minutes at ambient temperature then 3 hours in an ice/NaCl/water bath. The solids were filtered, washed with 25 mL of 5:1 hexanes: EtOAc, and dried under vacuum to afford the title compound (19.48 g) as white crystals. A second crop of crystals (2.28 g) was obtained from the filtrate.

(d) (1SR, 4SR, 5RS, 6SR)-Ethyl 4-(spiro-5'-hydantoin)-2-oxabicyclo[3.1.0]hexane carboxylate. To a slurry of ammonium carbonate (5.65 g, 58.8 mmol), potassium cyanide (2.01 g, 30.9 mmol) in 25 mL of methanol at ambient temperature was added a solution of the product of step (c) (5.0 g, 29.4 mmol) in 25 mL of methanol. The mixture was stirred at ambient temperature and monitored by HPLC. After 23 hours the reaction was complete. The mixture was diluted with 100 mL of water, cooled and seeded. The pH was adjusted from 9.6 to 7.0 with 6 N hydrochloric acid giving a white solid. The slurry was stirred at 0-5°C for 1.5 hours, filtered and washed with 75 mL of cold water-methanol (2:1). The white solid was dried *in vacuo* at 40°C affording the title compound (5.55 g, 78.6%). The product was identified by ^1H NMR.

(e) (1SR, 4SR, 5RS, 6SR)-4-(spiro-5'-hydantoin)-2-oxabicyclo[3.1.0]hexane carboxylic acid. A solution of the product of step (d) (7.59 g, 31.6 mmol) in 2N NaOH (63.2 mL) was stirred for 30 minutes at ambient temperature. The hydrolysis was then quenched by the addition 12N HCl (5.27 mL, 63.2 mmol). The reaction mixture was then stirred for three hours at 0°C, then vacuum filtered. The solid collected was dried under vacuum at 50°C overnight,

affording the title compound (6.12 g, 91.3%). ^{1}H NMR (DMSO-d_6) δ 2.24 (s, 1H), 2.26 (s, 1H), 3.35 (d, 1H, J = 11Hz), 4.05 (d, 1H, J = 11Hz), 4.39 (d, 1H, J = 5 Hz). ^{13}C NMR (DMSO-d_6) δ 22.14, 30.75, 65.74, 68.32, 70.61, 156.32, 171.11, 175.63. Anal Calcd for $C_8H_8N_2O_5$: C, 45.29; H, 3.80; N, 13.2. Found: C, 45.02; H, 3.75; N, 12.92.

(f) 1R, 4R, 5S, 6R-(-)-4-spiro-5'-hydantoin-2-oxabicyclo[3.1.0]hexane carboxylic acid, (R)-(-)-2-phenylglycinol salt. To the product of step (e), (0.80 g, 3.8 mmol) was added (R)-(-)-phenylglycinol (0.52 g, 3.8 mmol) in ethanol (20 mL) and water (4 mL). The mixture was heated to reflux, and an additional 1 mL of water was added, producing a homogenous solution. After approximately 30 minutes at reflux, the mixture was allowed to cool to ambient temperature. After stirring at ambient temperature overnight, the reaction mixture was filtered, washed with 1 mL of a cold 25:5 mixture of ethanol and water, and dried under vacuum at 50°C overnight, to afford the title compound (0.57 g, 43.3%) as a white solid. ^{1}H NMR (DMSO-d^6) δ 2.05 (t, 1H, J = 3.3 Hz), 2.20 (d, 1H, J = 3Hz), 3.30 (d, 1H, J = 11Hz), 3.50 (m, 1H), 3.55 (m, 1H), 4.0 (d, 1H, J = 11Hz), 4.1 (m, 1H), 4.18 (d, 1H, J = 6Hz), 7.25 (m, 1H), 7.30 (m, 2H), 7.35 (m, 2H). Enantiomeric excess was determined to be 98.8% by HPLC.

(g) 1R, 4R, 5S, 6R-(-)-4-Amino-2-oxabicyclo[3.1.0]hexane-4,6-dicarboxylic acid. To the product of step (f) (1.0 g, 2.86 mmol) was added 15 mL (30 mmol, 10 eq) of 2M aqueous sodium hydroxide. The solution was heated at reflux for 43 hours. The resulting mixture was allowed to cool to ambient temperature, then extracted with CH_2Cl_2 (5 x 30 mL). The aqueous layer was diluted with 10mL of H_2O and acidified to pH2 with 3M HCl. The cloudy mixture was filtered, and the pH was adjusted to 8 using 2M NaOH, then the solution was allowed to stand over the weekend. This resulted in formation of a gel from the remaining silicic acid. The gel

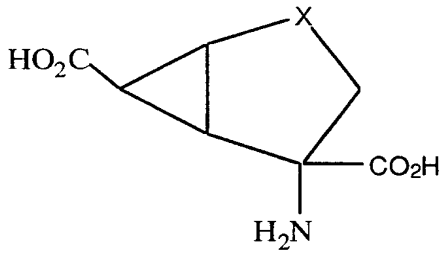
was removed by filtration through a medium glass frit over 1 hour and rinsed with 50 mL of H_2O.

An ion exchange column was prepared from 25 g of Bio-Rad AG 1-X8, 100-200 mesh, acetate form, resin. The resin was transferred to a gravity flow column using deionized H_2O and washed sequentially with 1M NaOH (2 x 50 mL) and H_2O (2 x 50 mL or until eluent neutral). The aqueous product solution was poured onto the resin in 50 mL portions. The column was washed sequentially with H_2O until the eluent was neutral (about 100 mL), 70 mL of 1:1 THF/H_2O, and 100 mL of H_2O. The product was eluted with 120 mL of a 1:3 mixture of acetic acid and H_2O. The entire eluent was collected in one flask and evaporated to 0.48 g of a white solid. The solid was slurried in 5 mL of H_2O and collected on a coarse glass frit. The flask was rinsed with additional H_2O (2 x 5 mL) and these rinsings were used to wash the collected solid. After drying under vacuum at 70°C for 18 hours, the title compound (0.33 g, 62%) was obtained as a white solid. The structure was confirmed by ^1H NMR and analysis.

Claims

1. A method of treating premenstrual dysphoric disorder, which comprises administering to a subject in need of treatment an effective amount of an agonist which acts at negatively-coupled cAMP-linked metabotropic glutamate receptors.

2. A method as claimed in Claim 1, in which the agonist is a compound of the formula



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in which X represents CH_2, O or S; or a pharmaceutically acceptable metabolically labile ester or amide thereof; or a pharmaceutically acceptable salt thereof.

3. A method as claimed in Claim 2, in which the agonist is selected from:

1S,2S,5R,6S-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid;

1SR,4SR,5RS,6SR-4-amino-2-oxabicyclo[3.1.0]hexane-4,6-dicarboxylic acid;

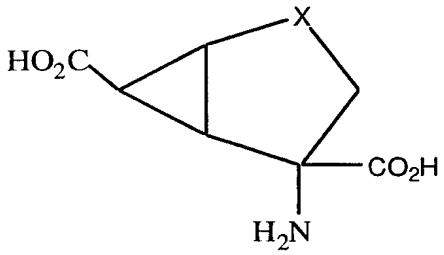
1SR,4SR,5RS,6SR-4-amino-2-thiabicyclo[3.1.0]hexane-4,6-dicarboxylic acid and

1R,4R,5S,6R-4-amino-2-oxabicyclo[3.1.0]hexane-4,6-dicarboxylic acid.

4. Use of an agonist which acts at negatively-coupled cAMP-linked metabotropic glutamate receptors for the

manufacture of a medicament for the treatment of premenstrual dysphoric disorder.

5. Use as claimed in Claim 4, in which the agonist is a compound of the formula



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in which X represents CH_2, O or S; or a pharmaceutically acceptable metabolically labile ester or amide thereof; or a pharmaceutically acceptable salt thereof.

6. Use as claimed in Claim 5, in which the agonist is selected from:

1S,2S,5R,6S-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid;

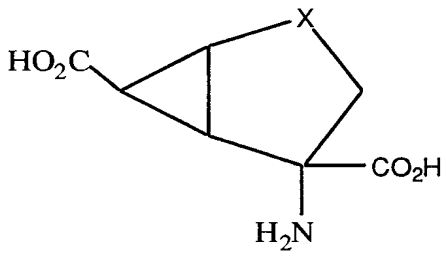
1SR,4SR,5RS,6SR-4-amino-2-oxabicyclo[3.1.0]hexane-4,6-dicarboxylic acid;

1SR,4SR,5RS,6SR-4-amino-2-thiabicyclo[3.1.0]hexane-4,6-dicarboxylic acid and

1R,4R,5S,6R-4-amino-2-oxabicyclo[3.1.0]hexane-4,6-dicarboxylic acid.

7. A pharmaceutical composition for use in the treatment of premenstrual dysphoric disorder which comprises an agonist which acts at negatively-coupled cAMP-linked metabotropic glutamate receptors.

8. A composition as claimed in Claim 7, in which the agonist is a compound of the formula



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in which X represents CH_2, O or S; or a pharmaceutically acceptable metabolically labile ester or amide thereof; or a pharmaceutically acceptable salt thereof.

9. A composition as claimed in Claim 8, in which the agonist is selected from:

1S,2S,5R,6S-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid;

1SR,4SR,5RS,6SR-4-amino-2-oxabicyclo[3.1.0]hexane-4,6-dicarboxylic acid;

1SR,4SR,5RS,6SR-4-amino-2-thiabicyclo[3.1.0]hexane-4,6-dicarboxylic acid and

1R,4R,5S,6R-4-amino-2-oxabicyclo[3.1.0]hexane-4,6-dicarboxylic acid.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/01344

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61K 31/38, 31/34, 31/195
US CL :514/443, 470, 561
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/443, 470, 561

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

HCAPLUS- compounds herein for any purpose

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96/04901 A1 (ELI LILLY AND COMPANY) 22 February 1996, entire document.	1-3 and 7-9
Y	EP 0 696 577 A1 (ELI LILLY AND COMPANY) 14 February 1996, abstract and page 3.	1-3 and 7-9
Y	LYGHT, C.E. et al. The Merck Manual of Diagnosis and Therapy (11th Ed.). Rahway, N.J.: Merck Sharp & Dohme Research Laboratories. 1966, pages 658-59.	1-3 and 7-9

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
10 APRIL 1998

Date of mailing of the international search report
04 JUN 1998

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703) 305-3230

Authorized officer
M. MOEZIE
Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)★

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/01344

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 4-6
because they relate to subject matter not required to be searched by this Authority, namely:

Claims drawn to the "use of" a compound or composition are non-statutory.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.